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Flexible Total Synthesis of (±)-Aureothin, a Potent Antiproliferative Agent

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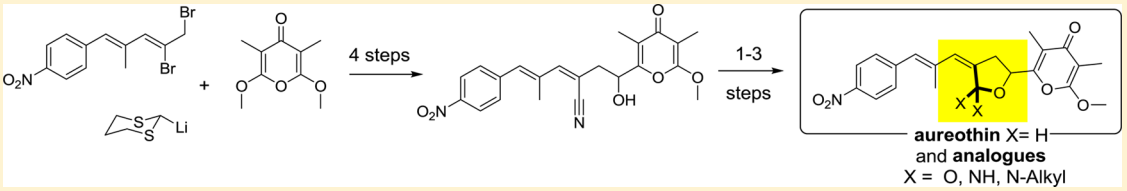
Supporting Information

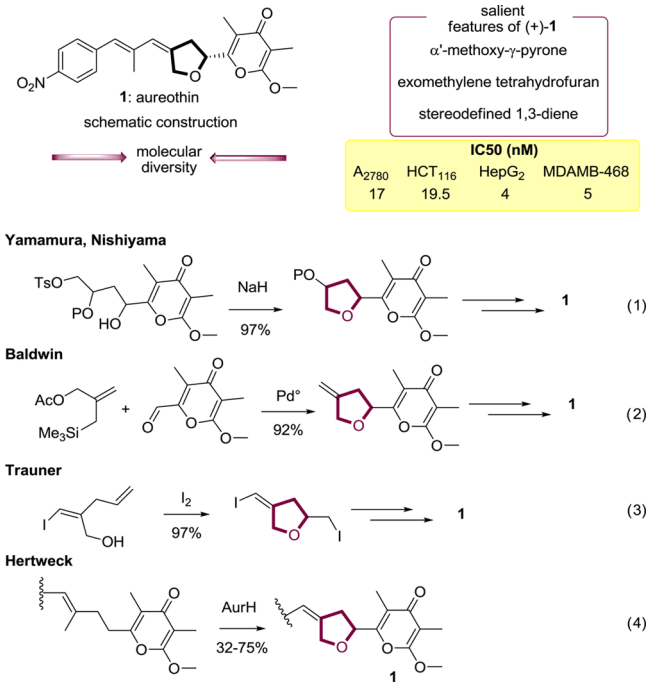


ABSTRACT: Amenable to late-stage preparation of analogues, a flexible and convergent total synthesis of (±)-aureothin is presented. The strategy was based on a desymmetrization of α,α′-dimethoxy-γ-pyrone by a process combining 1,4-addition and alkylation of vinylogous enolate to stereoselectively reach the backbone of the target. Palladium-catalyzed cyanation of an elaborated and isomerizable *E,Z* dienyl motif followed by Pinner cyclization enabled the construction of the tetrahydrofuran motif while a first approach based on a late-stage oxidation was unsuccessful.

I. INTRODUCTION

Isolated in 1953, it is only recently that aureothin (**1**), a polyketide metabolite of *Streptomyces thioluteus*, significantly attracted the attention of the scientific community involved in synthetic and biomolecular chemistry (Scheme 1).[1−6] Of moderate complexity but structurally dense, the molecule combines α′-methoxy-γ-pyrone and stereodefined 1,3-diene scaffolds connected to an unusual nitroaryl and a chiral tetrahydrofuran appendage. The stereo- and enantioselective synthesis of these structural elements is not trivial and relates to other natural products and applications.[7] As a substantial incentive, aureothin (**1**) is supposedly endowed with antitumoral, antifungal, antiparasitic, and pesticidal activity[8] displaying significant selectivity against trypanosome strains.[9] As a matter of fact, we found that (+)-**1** exhibits potent and selective antiproliferative activity (IC_{50} respectively 17, 19.5, 4, and 5 nM) against four cancer cell lines: A2780 (ovarian), HCT116 (colon), HepG2 (liver), and MDAMB-468 (breast).[10] This makes aureothin (**1**) an attractive lead molecule and underscores the need for synthetic routes to analogues.

Scheme 1. Aureothin, Antiproliferative Activity, and Previous Approaches to the THF Core



The pioneering studies of Yamamura,[2] Baldwin,[3] Trauner,[4] and Hertweck[5] unveiled interesting approaches to **1**. However, the construction of the tetrahydrofuran ring (eqs 1−3), occurring in the early stages of the synthetic routes, does not lend to the easy preparation of analogues with a decorated heterocycle. Likewise, access to such molecules seems challenging using enzymes due to the reactivity of AurH (eq 4).[11] Indeed, the cytochrome performs the heterocyclization of the precursor of **1** by a double C−H oxidation that prevents the interception of intermediates suitable for analogues preparation.

We recently introduced a new strategy to access natural products containing the α′-methoxy-γ-pyrone scaffold warranting an asymmetric synthesis of (+)-**1** with the expedient preparation of **5a** by one-pot condensation of **2** with 2-lithio-1,3-dithiane and diene **4a** (Scheme 2).[12] As the last step, P450 mediated C−H oxidation of racemic alcohol **5a** produced a

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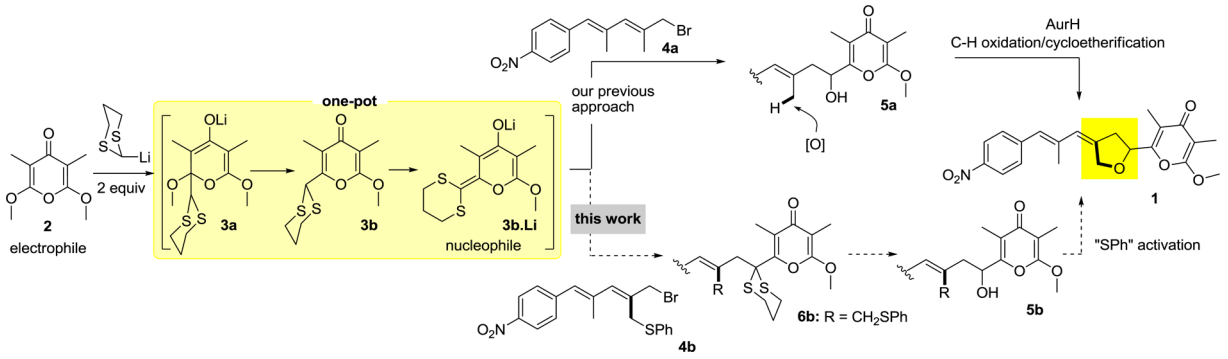
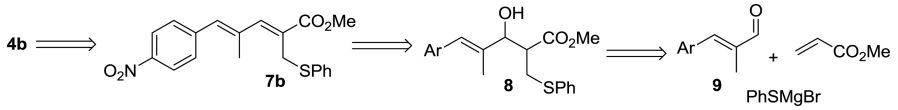
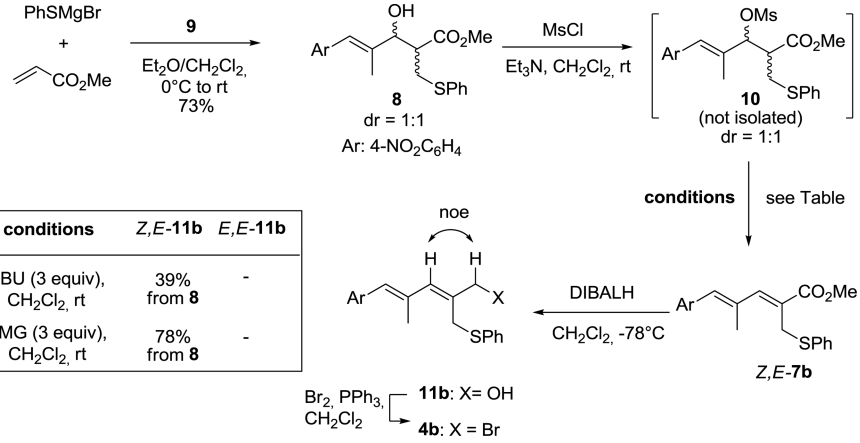
Scheme 2. Previous Access to Aureothin and New Synthetic Approach



Scheme 3. Retrosynthesis of 4b



Scheme 4. Stereoselective Synthesis of 4b



conditions	*Z,E*-**11b**	*E,E*-**11b**
DBU (3 equiv), CH_2Cl_2, rt	39% from **8**	-
TMG (3 equiv), CH_2Cl_2, rt	78% from **8**	-

dihydroxylated intermediate from one of the enantiomers which spontaneously cyclized, forging the tetrahydrofuran ring of aureothin (**1**).

The HPLC analysis of synthetic aureothin (**1**) required the preparation of *rac*-**1** for comparison and rigorously establishing the enantiopurity of the material. In order to produce a sample of racemic materials, the racemization of (+)-**1** was undertaken under basic or acidic conditions, which seemed the shortest route to this material that could also be pertinent for biological evaluations. Despite a report of prompt racemization of (+)-aureothin (**1**),[13] the production of racemic materials from (+)-**1** turned out to be more troublesome than anticipated. Basic or acidic conditions applied to (+)-**1** failed to produce (±)-**1** which prompted us to seek a synthetic alternative. Although concise and convergent, our initial pathway could not provide such material due to the enantiodiscrimination of AurH. Consequently, we seized the opportunity to establish a synthetic route, not only to the target but also to analogues. We report herein a synthesis of (±)-**1** suitable for the late-stage preparation of analogues with a decorated tetrahydrofuran scaffold targeting the core of the target. Noteworthy, our new approach complements the aforementioned synthetic pathways enabling the preparation of original molecules.

II. RESULTS AND DISCUSSION

A. First Strategy. As outlined in Scheme 2, our initial strategy involved nucleophilic addition to α,α'-dimethoxy-γ-pyrone **2** producing in fine vinylogous enolate **3b.Li** a cornerstone for assembling the side chain of the target with the α'-methoxy-γ-pyrone motif.[14] Thorough investigation revealed that intermediate **3b.Li** is the result of a sequence of transformations including an unusual and selective 1,4-addition to **2**, lithium methoxide elimination of **3a**, and deprotonation of **3b**.[15]

Provided that stereodefined *E,E*-**4b** can be assembled with enolate **3b.Li**, dithiane hydrolysis of the resulting **6b** and reduction of the resulting ketone would lead to **5b** and then aureothin (**1**) after heterocyclization by activation of the phenylthioether moiety (Scheme 2). Even if electrophiles **4a** and **4b** are structurally close, it was not clear whether the more hindered **4b** would react with the vinylogous enolate **3b.Li**.

To investigate this point, we began the assemblage of the highly functionalized diene **4b** using the methodology described by Shono in which the tandem aldolisation of aldehyde and Michael acceptors was triggered by magnesium thiolates functioning as a linchpin.[16] Applied to the readily available enal *E*-**9**, this chemistry would warrant a route to aldol **8** that would be elaborated into diene **7b** by dehydration

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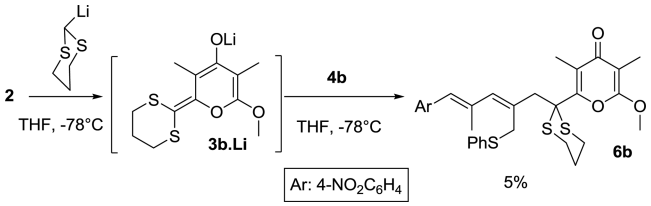
followed by reduction of the ester and bromation of the resulting alcohol (Scheme 3).

As detailed in Scheme 4, this plan was smoothly implemented producing **8** in 73% yield although without stereoselectivity (dr = 1:1). This proved to be inconsequential for the preparation of both ester *Z,E*-**7b** and alcohol *Z,E*-**11b** as long as a nucleophilic base such as 1,1,3,3-tetramethylguanidine (TMG) was employed to promote the elimination of mesylate **10**. While 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was unreactive toward one of the diastereoisomer of **10**, the conversion of a mixture of both isomers into one isomeric diene *Z,E*-**7b** was successfully carried out in the presence of TMG. The subsequent reduction of ester *Z,E*-**7b** furnished alcohol *Z,E*-**11b** in 78% yield (three steps). The configuration of the diene unit was then conveniently confirmed by 2D ^{1}H NMR spectroscopy, and it is worth noting that *E,E*-**11b** was not produced. A rationale for such selectivity probably entailed the substitution of one diastereoisomer of mesylate **10** with TMG, promoting *anti*-elimination of the resulting guanidinium intermediate.

An initial attempt to couple enolate **3b.Li** with **4b**, prepared by bromation of alcohol **11b**, was met with disappointing results, the resulting adduct **6b** being isolated in 5% yield among the remaining starting materials and unidentified products (Scheme 5). This outcome could not be enhanced

Scheme 5. Assemblage of 6b



after screening additives (HMPA), conditions (temperature, time), and the nature of the leaving group (OMs instead of Br) and after an attempt to diminish the steric hindrance of **4b** (SEt instead of SPh).

After the excessive steric hindrance of both **3b.Li** and **4b** was suspected to account for the failed coupling, the strategy was adjusted. We anticipated that the assemblage of **4b** with a less hindered nucleophile would be more efficient. Obtained by deprotonation of α-methyl-α'-methoxy-γ-pyrone **12**, a known pronucleophile prepared by reductive treatment of **3b**, enolate **12.Li** appeared to be a suitable candidate (Scheme 6). In case of success, **13b** had to be further oxidized at the γ-position for which the formation of an enolate would provide a solution.[17] This strategy could deliver alcohol **5b** not only as a racemate but also as an enantioenriched compound, providing the use of chiral oxidant.

Capitalizing on the first strategy, the coupling of enolate **12.Li** with **4b** was carried out at −100 °C furnishing **13b** in 49% yield (60% conversion, 80% brsm) along with 2% of the isomeric adduct (not shown) resulting from the S_N2' pattern of reaction. This side product was isolated in 18% yield when the coupling was conducted at −78 °C.

With the full carbon backbone of aureothin assembled, we investigated the key γ-oxidation of **13b** to produce **5b** (Scheme 7). Being of higher reactivity, the vinylogous enolate of **13b** was expected to react selectively toward an oxidant compared to phenylsulfide and 1,3-diene moieties contained in **13b**. To selectively induce enolization and oxidation, strong bases (LDA, *n*-BuLi, KHMDS, LiHMDS, KH) were tested in combination with an oxidant such as O_2, $(PhCO_2)_2$, or the Davis oxaziridine reagent **14**. Unsuccessful, this screening of conditions led only to the recovery of starting materials, its decomposition, or the occasional oxidation of the phenylsulfide or of the α'-methoxy-γ-pyrone scaffold. Having described a metal-free methodology for the γ-oxidation of cyclic enone with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under an atmosphere of O_2 (PhMe, 120 °C), we also explored such conditions to perform the oxidation of **13b**.[18] As the sole result, a slow decomposition of the starting materials was observed.

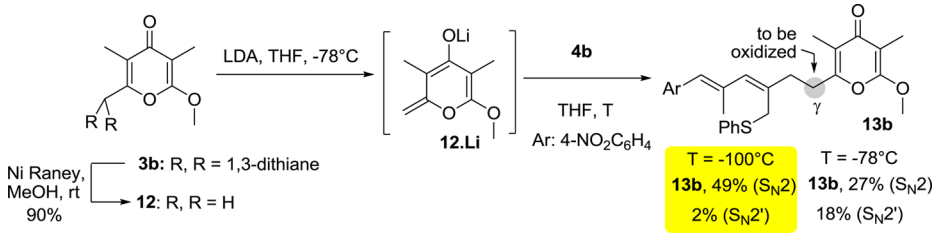
In order to assess the feasibility of this key transformation, we undertook the γ-oxidation of deoxyaureothin **13a** which was structurally close to **13b** but less hindered since it was deprived of the phenylsulfide substituent (Scheme 8). Resulting from the coupling of **12.Li** with **4a**, **13a** was produced in 60% yield. Exposure of this compound to LiHMDS was followed by the introduction of oxaziridine reagent **14** providing alcohol **5a** in 76% yield. Although selective γ-oxidation of **5a** occurred, only modest enantioselectivity (35% ee) was measured. Yet, it is worth noting that alcohol **5a** is a direct precursor of (+)-**1** upon exposure to AurH.

In stark contrast with **13a**, similar treatment of **13b** led to a complex mixture of products from which it appeared the α'-methoxy-γ-pyrone scaffold was oxidized (Scheme 9). This suggested that the phenylsulfide substituent may hinder the γ-position, preventing the formation of the corresponding enolate or the approach of the oxidant. To ascertain the formation of enolate **13b.Li**, quenching experiments involving D_2O were conducted but inconclusive data were collected.[19] At any rate, the γ-oxidation of **13b** was not performed and an adaptation of our strategy was required.

In answer, another access to **5b** was explored. Entailing the soft enolization of the α'-methoxy-γ-pyrone scaffold to access silyl enol ether **15**, the strategy included the regioselective epoxidation of **15** to induce vinylogous Rubottom oxidation by fragmentation of silyl epoxide **16** (Scheme 10).[20]

Unfortunately, treatment of **13b** with TBSOTf or TMSOTf and Et_3N at 0 °C (CH_2Cl_2, 20 min) led to demethylated

Scheme 6. Construction of 13b from 12



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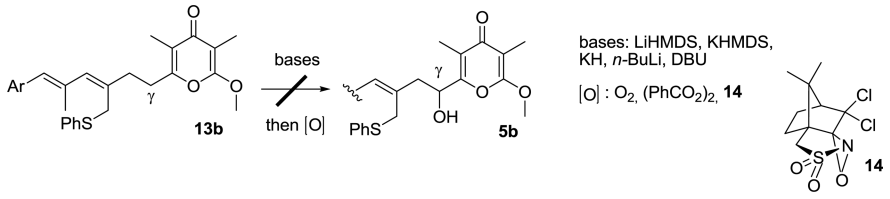
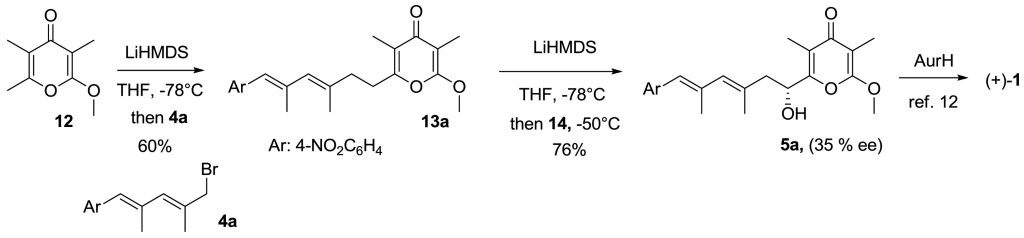
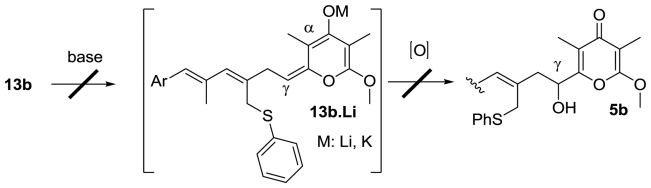
Scheme 7. Attempts To Promote γ-Oxidation of 13b



Scheme 8. Assemblage and γ-Oxidation of Deoxyaureothin 13a



Scheme 9. Attempts To Generate Enolate 13b.Li

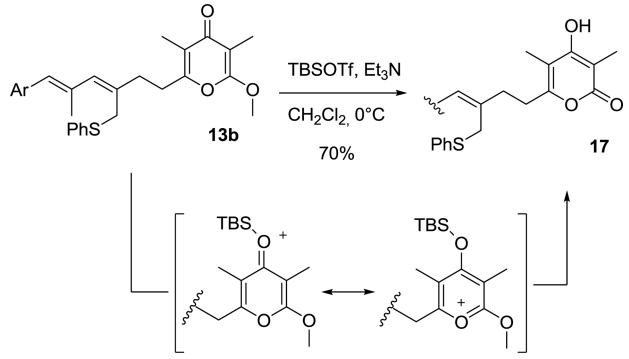


product **17** (Scheme 11). Surmising that Et_3N acted as a nucleophile instead of base toward an electron-deficient intermediate as depicted in Scheme 11, we switched the base to the more hindered iPr_2EtN to avoid the demethylation reaction of the α′-methoxy-γ-pyrone scaffold. As indicated by the monitoring of the experiment by ^1H NMR spectroscopy, the demethylation of **13b** was prevented. Still, the desired product **15** was not observed, and when an oxidant (*m*-CPBA containing water) was introduced to the reaction mixture, several products were obtained from which **17** was identified, its formation arising probably from the hydrolysis of the γ-pyrone scaffold.

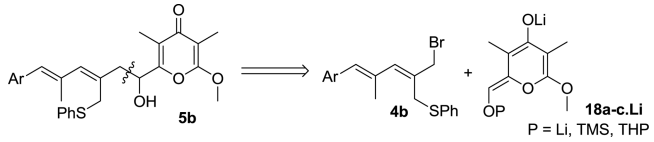
In view of the difficulties encountered in achieving the γ-oxidation of **13b**, we directed our efforts toward an alternative strategy embedding the coupling of vinylogous enolates **18a-c.Li** with the side chain **4b** (Scheme 12). Since these species have the desired level of oxidation, this retrosynthetic analysis could provide a concise access to **5b** in the case of successful assemblage.

Disappointingly, another dead-end was met since under no conditions (LDA, LDA/TMEDA, *n*-BuLi/TMEDA, *t*-BuLi/TMEDA) was the formation of **18a−c.Li** accomplished from the corresponding alcohol, silyl ether, or acetal using either **4b** or D_2O as electrophiles to evidence the generation of the corresponding enolate.

Scheme 11. Attempts To Form the Silyl Enol Ether of 13b Led to Demethylated 17



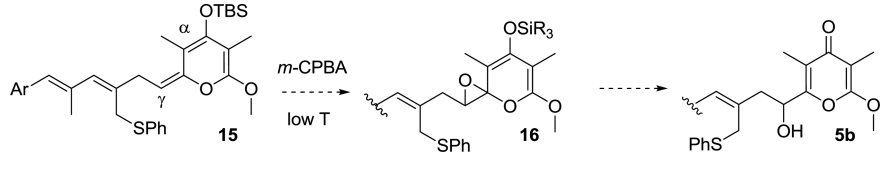
Scheme 12. Last-Effort Retrosynthesis of 5b (TMS: Trimethylsilyl, THP: Tetrahydropyrane)



Unable to further functionalize **13b** or to improve the process leading to **6b**, we reasoned that side chain **4b** was excessively hindered in allowing completion of the synthesis of aureothin (**1**).

B. Second Strategy. Accordingly, we devised a strategy in which vinylogous enolate **3b.Li** would be assembled with the less hindered dibromodiene **4c** to furnish **6c** (Scheme 13). Harnessing the C−Br bond of the resulting bromodiene **6c**, by a metal−bromide exchange reaction for instance, would lead, after treating the generated nucleophile with formaldehyde, to

Scheme 10. Alternative Strategy to Reach 5b via Rubottom-like Oxidation



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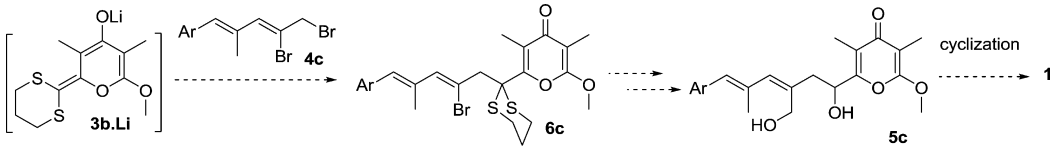
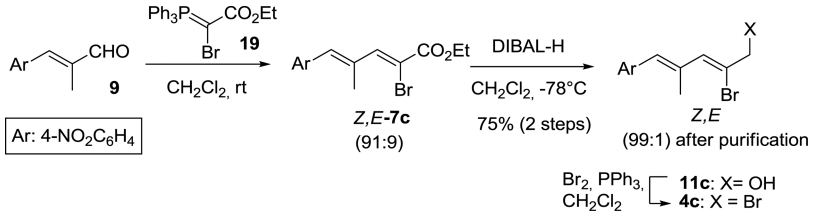
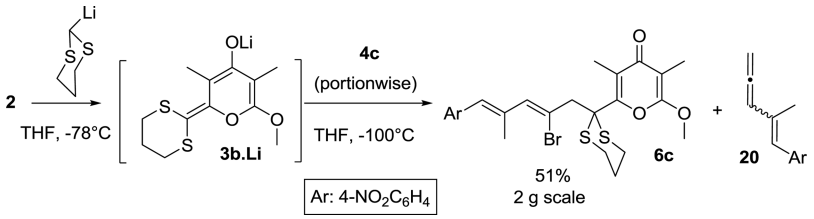
Scheme 13. Alternative Synthetic Route to 1



Scheme 14. Stereoselective Synthesis of 4c



Scheme 15. Optimized Conditions for Preparing 6c



diol **5c**, a short-lived intermediate of the enzymatic process that has never been isolated. Provided that the inherent reactivity of allylic alcohol facilitates the cyclization, diol **5c** would readily be converted into **1**.

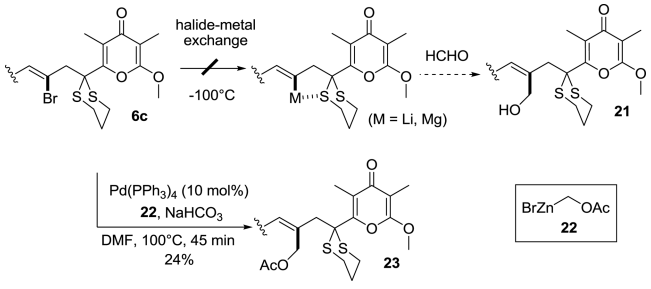
As shown in Scheme 14, the preparation of the electrophile **4c** began by a stereoselective olefination of enal *E*-**9** with bromophosphane **19** to give *Z,E*-**7c** in good yield and selectivity (*Z,E*:*E,E* = 91:9).[21] If such selectivity was known with enals, the methodology was scarcely reported with α,β-disubstituted enals that lead to tetrasubstituted 1,3-dienes.

Reduction of the ester produced *Z,E*-dienol **11c** in 75% yield (two steps) that was suitable for confirmation of the diene configuration by 2D NMR spectroscopy. Pleasingly, **11c** was isolated without any contamination of the isomeric *E,E*-dienol. Hence, this expeditious sequence provided an entry into stereodefined trisubstituted 1,3-diene, ready for further synthetic manipulations.

In order to study the key coupling outlined in Scheme 2, alcohol **11c** was converted into the rather unstable dibromodiene **4c** and, upon reaction with **3b.Li**, initially furnished the adduct **6c** in only 8% yield. As indicated by the production (ca. 20% yield) of allene **20**, the sensitivity of dibromodiene **4c** called for significant optimization of the initial protocol (Scheme 15). In contrast to our previous strategy involving hindered **4b**, we felt that the sensitivity of **4c** to basic conditions could be overridden. Hence, performing the alkylation of **3b.Li** at −100 °C furnished **6c** in 16% yield while portionwise addition of **4c** enhanced the yield to 32%. Eventually, the best result was achieved with a slight excess of **3b.Li** reacting with crude **4c**. Hence, the highly substituted diene **6c** was constructed in 51% yield from alcohol **11c** on 2 g scale upon treatment of **2** (1.4 equiv) with 2-lithio-1,3-dithiane (2.8 equiv) at −78 °C followed by the portionwise addition of **4c** (1 equiv) at −100 °C. Notably, the process encompasses key transformations such as 1,4-addition of 2-lithio-1,3-dithiane and the chemo- and regioselective alkylation of **3b.Li** with the highly substituted and base-sensitive dibromodiene **4c**.

Once a reliable access to **6c** was secured, setting the methylene alcohol in **21** was envisaged by a metal−bromide (Li, Mg) exchange reaction followed by trapping of the metalated diene with formaldehyde (Scheme 16). This strategy

Scheme 16. Synthetic Transformations of Bromodiene 6c



had the supposed advantage of preventing the isomerization of the dienyl motif by coordination of the metal with the dithiane group. However, the decomposition of **6c** was only observed under the conditions applied for the preparation of **21**. Consequently, we resorted to utilizing palladium-catalyzed couplings to install the methylene alcohol. Among the available synthetic methodologies, Negishi coupling of bromodiene **6c** with organozinc bromide **22**, a surrogate of formaldehyde, appeared straightforward for establishing the desired C−C bond of **23**, even though this reagent has scarcely been employed for such couplings.[22]

Despite extensive screening of conditions to improve the process, the preparation of **23** remained unsatisfactory with yields reaching 24%, this disappointing outcome being probably due to the sensitivity of the α'-methoxy-γ-pyrone scaffold toward nucleophiles.[23] To perform this transformation more

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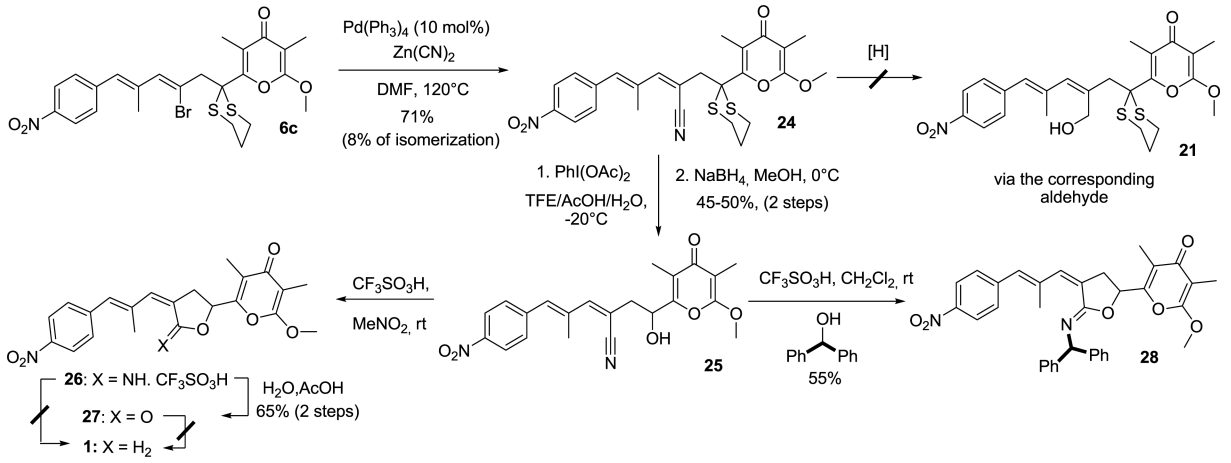
Scheme 17. Cyanation of Diene 6c Giving Access to Cyclic Compounds 26−28

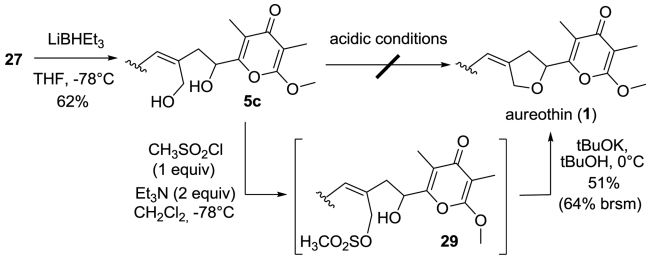


efficiently, we considered carbon monoxide or cyanide anions as alternative nucleophiles.[24] Anticipating that the 1,3-cyanodiene adduct would be less prone to isomerization, we opted for the cyanation of **6c** over the carbonylation to preserve the configurational integrity of the *Z,E*-dienyl motif (Scheme 17). Pleasingly, the conversion of **6c** into cyanodiene *Z,E*-**24** (71% yield) was successfully achieved with the aid of tetrakis(triphenylphosphine)palladium and $Zn(CN)_2$ under conditions strongly limiting the formation of *Z,Z*-**24** (8% yield).[25] Importantly, the desired cyanodiene was isolated without any isomeric contamination.

To our knowledge, this showcases a rare and challenging palladium-catalyzed cyanation of stereodefined 1,3-diene particularly prone to isomerization.[26] To install the corresponding methylene alcohol of **21**, we attempted to convert cyano **24** into the corresponding aldehyde by partial reduction to imine followed by hydrolysis. This route turned out to be unsatisfactory from the first stage, and alternative strategies were examined. One of them, a 5-exo-dig cyclization, relied on both the electrophilic character of the nitrile and the anchimeric assistance of the hydroxyl, at this stage masked by the dithiane moiety. To carry out this strategy, the 1,3-dithiane moiety of **24** was then hydrolyzed and the resulting ketone was reduced to alcohol **25**.[27] Surprisingly, all attempts to elicit the 5-exo-dig cyclization of **25** under basic conditions gave disappointing results.[28] Consequently, this transformation was attempted upon acidic treatment of **25** with the hope to accomplish a formal Pinner cyclization. While this choice seemed counter-intuitive given the risk of dehydration of alcohol **25**, treatment of this compound with trifluoromethanesulfonic acid (5 equiv) ensured complete conversion into iminium ether **26** in 3 h at ambient temperature.[29,30] If the iminium salt of **26** was stable under these conditions, neutral iminoether **26** was extremely sensitive, being basic and nucleophilic, and required hydrolysis into lactone **27** (65% yield, two steps) prior to any attempt of isolation. One might note that **27** is a structurally close analogue of aureothin (**1**) with a different polarization of the 1,3-diene motif. While it seems that the Pinner cyclization of cyanodiene is unreported, the success of this transformation with **25** is remarkable considering the strength of the acid and given the potential side-reactions such as dehydration or isomerization of the 1,3-diene motif. Moreover, applying Ritter conditions to **25**, which encompass acidic ionization of a secondary alcohol, in the presence of diphenylmethanol led to iminoether **28** (55% yield), resulting in the grafting of the alcohol scaffold to aureothin.[31] Since product **28** was stable and isolated, an innovative and modulable path to original analogues was enabled. Electronic and steric variations at the core of aureothin (**1**) were now attainable in a concise and late-stage fashion.

To complete the total synthesis, it was tempting to reduce cyclic iminium ether **26** or lactone **27** to the corresponding cyclic ether. Unfortunately, all attempts to induce the reductive conversion of **26** or **27** into aureothin (**1**) were unsuccessful. On the other hand, the reduction of lactone **27** with $LiBHEt_3$ provided diol **5c** (Scheme 18), a promising candidate not only

Scheme 18. Synthesis of Aureothin (1)



to complete the synthesis of **1** but also to access analogues. Accordingly, heterocyclization of **5c** was initially attempted by activation of the allylic alcohol with Brønsted or Lewis acids. Strikingly though, none of these conditions elicited the formation of the tetrahydrofuran ring. Adapting the strategy, the cyclization of **5c** was examined after activation of the hydroxyl as mesylate.

For this purpose, diol **5c** was regioselectively converted into **29** that did not cyclize spontaneously, the cyclization requiring the successive addition of tBuOK to produce aureothin (**1**) in 64% yield (brsm) from **5c**.

III. CONCLUSION

A new approach to (±)-**1** has been established by extending our convergent strategy further. Decreasing the steric hindrance of the electrophile reacting with vinylogous enolate **3b.Li** allowed the preparation of the advanced and versatile bromodiene **6c**. The additional features of our strategy en route to (±)-**1** include the stereoselective assemblage of a highly substituted and isomerizable conjugated cyanodiene and the smooth construction of the exomethylene tetrahydrofuran

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ring upon acidic treatment. This study provides perspectives when investigating the potent antiproliferative activity of aureothin (**1**) while providing a stereoselective synthetic route of 11 steps (2%) from 4-nitrobenzaldehyde.[32]

More importantly, our efforts opened an even shorter route to cyclic and acyclic analogues that were not attainable with previous strategies. Indeed, diol **5c**, lactone **27**, and alkylated imino ether **28** are now readily accessible as late-stage analogues of aureothin, enabling the decoration of the tetrahydrofuran scaffold for pharmacological examination.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in deuterated chloroform relative to $(CH_3)_4Si$ and $CDCl_3$ respectively. Low resolution mass spectra were recorded using electrospray (ESI) or chemical (CI) ionization techniques. High-resolution mass data were recorded on a Q-TOF instrument with an electrospray source in APCI, EI, or ESI mode. Visualization was accomplished with UV (254 nm), $KMnO_4$, and 2,4-dinitrophenyl hydrazine (2,4-DNPH, 5% in HCl 2 M) staining solutions. All reactions requiring anhydrous conditions were performed in an oven (120 °C) and/or heat gun dried glassware under an atmosphere of desiccated argon. CH_2Cl_2 was distilled from CaH_2, THF was distilled from sodium/benzophenone, and argon was passed through a pad of anhydrous $CaSO_4$/crystals of silica gel prior to use. (1-Methoxycarbonylethylidene)triphenylphosphorane was synthesized by the reaction of triphenylphosphine with methyl 2-bromopropionate in CH_2Cl_2 and used without further purification. tBuLi (1.6 M in hexanes or 1.7 M in pentane) was titrated using a known amount of *N*-Boc-aniline in the presence of 1,10-phenanthroline in THF at 0 °C. Melting points were determined using a Kopfler hot stage apparatus and were uncorrected. Aldehyde *E*-**9**,[12] γ-pyrone **12**,[14] deoxyaureothin (**13a**),[6a] and alcohol **5a**[12] are known compounds.

(E)-Methyl 3-Hydroxy-4-methyl-5-(4-nitrophenyl)-2-(phenylthiomethyl)pent-4-enoate ***8/8′***. A MeMgBr solution (4.76 mL, 2.2 M in pentane, 10.47 mmol, 1.1 equiv) was diluted in anhydrous Et_2O (10 mL) under an argon atmosphere in a 100 mL single necked round-bottom flask. The flask was cooled to 0 °C, and a diluted solution of PhSH (1.15 g, 1.07 mL, 10.47 mmol, 1.1 equiv) in anhydrous Et_2O (10 mL) was added dropwise with a syringe. The mixture was stirred for 10 min at this temperature. Then a solution of **9** (1.82 g, 9.52 mmol, 1 equiv) and methyl acrylate (0.9 g, 0.94 mL, 10.47 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (12 mL) was added dropwise with a syringe at 0 °C. The heterogeneous brown solution was then allowed to warm to rt and was stirred for another 3 h. The reaction was quenched by addition of 50 mL of 10% citric acid aqueous solution, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were washed with brine, dried ($MgSO_4$), and evaporated under vacuum. The residue containing a mixture of two diastereoisomers was purified by flash chromatography on silica gel (pentane/EtOAc, 4:1) to yield **8** (orange oil, 1.35 g, 36.5%) and **8′** (orange powder, 1.35 g, 36.5%). The separation of **8** and **8′** was not required, and the mixture could be engaged in the next step. R_f = 0.30 (pentane/EtOAc, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (s, 3H), 2.97 (dt, J = 8.6, 5.2 Hz, 1H), 3.21−3.34 (m, 2H), 3.69 (s, 3H), 4.49 (d, J = 5.2 Hz, 1H), 6.66 (s, 1H), 7.20−7.40 (m, 5H, Ph), 7.38 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 31.2, 49.7, 51.9, 76.8, 123.2 (2C), 124.9, 126.4, 128.8 (2C), 129.3 (2C), 129.9 (2C), 135.1, 141.0, 143.7, 145.8, 173.1; IR (ν/cm^{-1}, neat): 3467, 2955, 1729, 1594, 1515, 1439, 1338, 1013; MS (APCI) m/z: 370 (M-H_2O+H)$^+$; HRMS: (APCI) calculated for $C_{20}H_{21}N_1O_5S$ (M − H)$^+$: 387.1140, found: 387.1140.

Data for **8′**: R_f = 0.20 (pentane/EtOAc, 4:1); Mp = 84 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (s, 3H), 3.00 (dt, J = 8.4, 5.9 Hz, 1H), 3.13−3.29 (m, 2H), 3.68 (s, 3H), 4.49 (t, J = 5.9 Hz,1H), 6.59 (s, 1H), 7.22−7.43 (m, 5H, Ph), 7.30 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 33.7, 48.8, 51.9, 76.7, 123.3 (2C), 125.2, 126.9, 128.9 (2C), 129.4 (2C), 130.6 (2C), 134.6, 141.3, 143.7, 146.0, 173.4; IR (ν/cm^{-1}, neat): 3443, 2949, 1702, 1590, 1514, 1437, 1343, 1023; MS (APCI) m/z: 370 (M − H_2O + H)$^+$; HRMS: (APCI) calculated for $C_{20}H_{21}N_1O_5S$ (M − H)$^+$: 387.1140, found: 387.1130.

(2Z,4E)-Methyl 4-Methyl-5-(4-nitrophenyl)-2-(phenylthiomethyl)-penta-2,4-dienoate ***7b***. The mixture **8**/**8′** (0.965 g, 2.49 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (25 mL) under an argon atmosphere in a 50 mL single necked round-bottom flask. Then Et_3N (0.50 g, 0.67 mL, 4.98 mmol, 2 equiv) followed by MsCl (0.43 g, 0.29 mL, 3.74 mmol, 1.5 equiv) was added at room temperature. The mixture was stirred at this temperature for 2 h 30 allowing the formation of mesylate **10**. 1,1,3,3-Tetramethylguanidine (0.86 g, 0.94 mL, 7.47 mmol, 3 equiv) was then added, and the mixture was stirred at rt for an additional 6 h. Saturated $NaHCO_3$ solution (25 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with 10% citric acid aqueous solution, and brine; dried ($MgSO_4$); and evaporated under vacuum yielding **7b** as an orange solid that was used for the next step without needed purification. R_f = 0.82 (pentane/EtOAc, 4:1); Mp = 78 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 3.79 (s, 3H), 4.03 (s, 2H), 6.62 (s, 1H), 7.19−7.43 (m, 6H), 7.30 (d, J = 8.7 Hz, 2H), 8.18 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 32.7, 52.3, 123.5 (2C), 127.3, 128.5, 128.9 (2C), 129.8 (2C), 131.7, 132.0 (2C), 135.5, 137.1, 143.2, 144.0, 146.5, 167.5; IR (ν/cm^{-1}, neat): 2942, 2844, 1709, 1597, 1507, 1340, 1267, 1169; MS (APCI) m/z: 370 (M + H)$^+$; HRMS: (APCI) calculated for $C_{20}H_{20}NO_4S$ (M + H)$^+$: 370.1113, found: 370.1119.

(2Z,4E)-4-Methyl-5-(4-nitrophenyl)-2-(phenylthiomethyl)penta-2,4-dien-1-ol ***11b***. To a stirred solution of crude ester **7b** (0.92 g, 2.49 mmol, 1 equiv) in anhydrous CH_2Cl_2 (25 mL) was added DIBAL-H (5.48 mL, 1 M solution in CH_2Cl_2, 5.48 mmol, 2.2 equiv) under argon at −78 °C. After 30 min, the reaction was quenched by the cautious addition of MeOH (1 mL) followed by the introduction of 1 M HCl solution (25 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were washed with brine, dried ($MgSO_4$), and evaporated under vacuum. The crude was purified by flash chromatography on silica gel (pentane/EtOAc, 4:1) to yield **11b** as an orange powder (0.66 g, 78% over three steps from **8**/**8′**). R_f = 0.27 (pentane/EtOAc, 4:1); Mp = 80 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87 (s, 3H), 3.87 (s, 2H), 4.33 (s, 2H), 6.18 (s, 1H), 6.44 (s, 1H), 7.18−7.38 (m, 5H, Ph), 7.32 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 33.5, 65.8, 123.3 (2C), 126.7, 127.6, 128.8 (2C), 129.4 (2C), 130.5 (2C), 132.6, 135.7, 136.4, 138.0, 144.1, 145.8; NMR 2D NOESY: see SI; IR (ν/cm^{-1}, neat): 3429, 2893, 1583, 1503, 1333, 1110, 1002; MS (APCI) m/z: 324 (M − H_2O + H)$^+$; HRMS: (ESI) calculated for $C_{19}H_{20}NO_3S$ (M + H)$^+$: 342.1164, found: 342.1162.

((2E,4E)-2-(Bromomethyl)-4-methyl-5-(4-nitrophenyl)penta-2,4-dienyl)(phenyl)sulfane ***4b***. PPh_3 (57 mg, 0.217 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (1 mL) under argon in a 10 mL, single necked, round-bottom flask, equipped with a magnetic stirring bar. Then Br_2 (11 μL, 0.217 mmol, 1 equiv) was added with a syringe at 0 °C, followed by alcohol **11b** (74 mg, 0.217 mmol, 1 equiv) dissolved in anhydrous CH_2Cl_2 (1 mL) under argon. After stirring for 10 min at this temperature, a solution of saturated $NaHCO_3$ (5 mL) was added to the organic solution. In a decantation funnel, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with brine and dried on Na_2SO_4. After removal of the volatiles under vacuum, an orange solid (150 mg) containing **4b** and PPh_3O was recovered and used without further purification in the next step. Compound **4b** was unstable but could be purified with significant loss of material by two sequential filtrations on silica gel (pentane/EtOAc, 4:1). R_f = 0.92 (pentane/EtOAc, 4:1);^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 3.97 (s, 2H), 4.28 (s, 2H), 6.26 (s, 1H), 6.41 (s, 1H), 7.20−7.40 (m, 5H, Ph), 7.33 (d, J = 8.8 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 33.7, 37.7, 123.4 (2C), 127.1, 128.8, 128.9 (2C, Ar), 129.6 (2C, Ar), 131.0 (2C, Ar), 133.9, 135.1, 136.6, 137.3, 143.6, 146.0; MS (APCI) m/z: 404 (M + H)$^+$.

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2-Methoxy-3,5-dimethyl-6-(2-((2Z,4E)-4-methyl-5-(4-nitrophenyl)-2- (phenylthiomethyl)penta-2,4-dienyl)-1,3-dithian-2-yl)-4H-pyran-4-one ***6b***. 1,3-Dithiane (47 mg, 0.394 mmol, 2 equiv) was dissolved in anhydrous THF (1.5 mL) under an argon atmosphere in a 10 mL single necked round-bottom flask. The flask was cooled to −78 °C, and *t*-BuLi (243 μL, 1.7 M in pentane, 0.414 mmol, 2.1 equiv) was added with a syringe. The deep yellow mixture was stirred for 10 min at this temperature. Then, pyrone **2** (36 mg, 0.197 mmol, 1 equiv) in solution in THF (2 mL) was added via a cannula over 10 min, and the mixture was stirred for 50 min at −78 °C during which time the solution became pale orange but remained limpid. Crude bromo **4b** (88 mg, 0.217 mmol, 1.1 equiv) in solution in THF (1 mL) was added via a cannula, and the mixture was stirred for 40 min at −78 °C. The reaction was quenched by addition of 5 mL of 10% citric acid aqueous solution, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layers were washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was purified by flash chromatography on silica gel ($MeNO_2/CH_2Cl_2$, 1:1) to yield impure **6b**. Further purification by preparative TLC (pentane/EtOAc, 1:1) yielded **6b** as a yellow oil (7 mg, 5%). R_f = 0.56 (pentane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 1.85 (s, 3H), 2.02 (m, 2H), 2.36 (s, 3H), 2.88 (m, 4H), 3.21 (s, 2H), 3.83 (s, 2H), 4.03 (s, 3H), 5.86 (s, 1H), 6.15 (s, 1H), 7.15−7.30 (m, 5H), 7.28 (d, J = 8.7 Hz, 2H), 8.18 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.0, 12.3, 18.6, 24.2, 28.9 (2C), 37.3, 44.9, 56.0, 57.4, 99.3, 122.3, 123.5 (2C), 127.2, 127.6, 129.0 (2C), 129.5 (2C), 131.3, 131.5 (2C), 135.3, 138.0, 138.2, 143.9, 146.1, 154.5, 161.7, 181.2; IR (ν/cm^{-1}, neat): 2923, 1652, 1593, 1515, 1341, 1316, 1166; MS (ESI) m/z: 596 (M + H)$^+$; HRMS: (APCI) calculated for $C_{31}H_{34}N_1O_5S_3$ (M + H)$^+$: 596.1599, found: 596.1590.

2-Methoxy-3,5-dimethyl-6-((3Z,5E)-5-methyl-6-(4-nitrophenyl)-3-(phenylthiomethyl)hexa-3,5-dienyl)-4H-pyran-4-one ***13b***. DIPA (21 mg, 29 μL, 0.211 mmol, 1.2 equiv) was diluted in anhydrous THF (0.5 mL) under an argon atmosphere in a 5 mL single necked round-bottom flask. The flask was cooled to −20 °C, and *n*-BuLi (114 μL, 2 M in hexanes, 0.229 mmol, 1.3 equiv) was added with a syringe. The mixture was stirred for 30 min at this temperature. The obtained LDA solution was then added to a solution of pyrone **12** (30 mg, 0.176 mmol, 1 equiv) in THF (0.5 mL) via a syringe at −78 °C. The mixture was stirred for 10 min at this temperature and then cooled to −100 °C. Crude bromo compound **4b** (71 mg, 0.176 mmol, 1 equiv) in solution in anhydrous THF (1 mL) was added via a syringe, and the mixture was stirred for 40 min, a period of time during which the temperature was maintained at −100 °C. The reaction was quenched by addition of 4 mL of 10% citric acid aqueous solution, and the aqueous layer was extracted with Et_2O (3 × 3 mL). The organic layers were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 1:1) to yield **13b** as a yellow oil (42 mg, 49% yield). R_f = 0.53 (pentane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (s, 3H), 1.85 (s, 3H), 1.96 (s, 3H), 2.65 (t, J = 7.5 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 3.81 (s, 2H), 3.96 (s, 3H), 5.90 (s, 1H), 6.33 (s, 1H), 7.20−7.35 (m, 5H), 7.30 (d, J = 8.7 Hz, 2H), 8.17 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.8, 10.0, 18.8, 29.7, 33.2, 36.1, 55.3, 99.4, 118.7, 123.5 (2C), 126.9, 127.3, 129.0 (2C), 129.5 (2C), 130.6 (2C), 133.7, 135.4, 135.7, 138.1, 144.1, 145.9, 157.0, 162.0, 180.8; IR (ν/cm^{-1}, neat): 2921, 1667, 1587, 1510, 1336, 1246, 1162;MS (APCI) m/z: 492 (M + H)$^+$; HRMS: (APCI) calculated for $C_{28}H_{30}N_1O_5S$ (M + H)$^+$: 492.1845, found: 492.1836.

2-((3E,5E)-3,5-Dimethyl-6-(4-nitrophenyl)hexa-3,5-dienyl)-6-methoxy-3,5-dimethyl-4H-pyran-4-one ***13a***. To a solution of **12** (85 mg, 0.505 mmol) in THF (5 mL) was added LiHMDS as a 1 M solution in THF (550 μL, 1.1 equiv, 0.550 mmol) at −78 °C. After 30 min at this temperature, **4a** (128 mg, 1.1 equiv, 0.550 mmol) was added dropwise as a solution in THF (2 mL). After 1 h at −78 °C, the reaction was quenched by addition of 10% citric acid aqueous solution, and the aqueous layer was extracted with AcOEt (3 × 10 mL). The organic layers were washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (AcOEt/Cyclohexane, 30:70 → 50:50) to yield **13a** (115 mg, 60%) as a yellow foam. R_f = 0.41 (pentane/AcOEt, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (s, 3H), 1.92 (s, 3H), 1.96 (s, 6H), 2.42 (t, J = 7.5 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 3.96 (s, 3H), 5.78 (s, 1H), 6.30 (s, 1H), 7.39 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.9, 10.0, 18.1, 19.2, 29.5, 37.8, 55.3, 99.4, 118.6, 123.5 (2C), 127.2, 129.4 (2C), 130.3, 136.7, 139.2, 144.6, 145.7, 157.4, 162.0, 180.9; HRMS (ESI) m/z calculated for $C_{22}H_{26}NO_5$ (M + H)$^+$: 384.1811, found: 384.1802.

2-((3E,5E)-1-Hydroxy-3,5-dimethyl-6-(4-nitrophenyl)hexa-3,5-dienyl)-6-methoxy-3,5-dimethyl-4H-pyran-4-one ***5a***. To a solution of **13a** (75 mg, 0.195 mmol) in THF (3 mL) was added LiHMDS as a 1 M solution in THF (430 μL, 0.429 mmol, 2.2 equiv) at −78 °C. After 30 min at this temperature, oxaziridine **14** (128 mg, 0.214 mmol, 1.1 equiv) was added. The reaction was warmed up to −20 °C over 30 min, and brine was added to quench the reaction. The aqueous layer was extracted with AcOEt (3 × 10 mL). The organic layers were washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was first purified by flash chromatography on silica gel (AcOEt/PE, 50:50 → 20:10) followed by preparative TLC (AcOEt/PE, 20:10) to yield **5a** (57 mg, 76%) as a yellow foam. HPLC analysis CHIRALCEL OD-H column, heptane/*i*PrOH, 90:10, 1 m/min flow rate, rt, 254 nm, t_R = 21.98 min (major), t_S = 26.50 (minor); 35% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.83 (s, 3H), 1.91 (s, 3H), 1.96 (s, 6H), 2.56−2.49 (m, 1H), 2.69−2.61 (m, 1H), 3.00 (br s, 1H), 4.02 (s, 3H), 4.98 (br t, 1H), 5.86 (s, 1H), 6.30 (s, 1H), 7.38 (d, J = 8.5 Hz, 2H), 8.18 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.3, 9.8, 18.9, 19.5, 25.95, 46.0, 55.9, 67.4, 100.2, 119.35, 123.9, 128.1, 129.85, 133.2, 134.0, 139.2, 144.8, 146.3, 156.8, 162.65, 181.3; MS (ESI) m/z: 400 (M + H)$^+$.

(Z)-4-Hydroxy-3,5-dimethyl-6-(4-(4-nitrophenyl)-3-(phenylthiomethyl)but-3-enyl)-2H-pyran-2-one ***17***. To a stirred solution of compound **13b** (30 mg, 0.061 mmol, 1 equiv) in anhydrous CH_2Cl_2 (1 mL) at 0 °C was added TBSOTf (32 mg, 28 μL, 0.122 mmol, 2 equiv) followed by Et_3N (19 mg, 25 μL, 0.183 mmol, 3 equiv). The mixture was allowed to stir for 10 min at 0 °C and was then quenched by the addition of a solution of saturated $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by preparative TLC (SiO_2, CH_2Cl_2/EtOAc, 2:1) to yield **17** (20 mg, 70%). R_f = 0.55 (CH_2Cl_2/EtOAc, 2:1); Mp = 49 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (s, 3H), 1.99 (s, 6H), 2.62 (t, J = 7.5 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H), 3.83 (s,2H), 5.90 (s, 1H), 6.36 (s, 1H), 7.20−7.36 (m, 5H), 7.32 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.4, 9.8, 18.9, 29.7, 33.9, 36.1, 55.3, 98.2, 106.5, 123.5 (2C), 126.8, 127.3, 129.0 (2C), 129.6 (2C), 130.7 (2C), 133.8, 135.6, 135.9, 138.4, 144.3, 145.9, 157.9, 163.9, 165.3; IR (ν/cm^{-1}, neat): 3205, 2922, 1667, 1571, 1513, 1340, 1232, 1109; MS (APCI) m/z: 478 (M + H)$^+$; HRMS: (ESI) calculated for $C_{27}H_{26}N_1O_5S$ (M − H)$^+$: 476.1532, found: 476.1552.

(2Z,4E)-Methyl 2-Bromo-4-methyl-5-(4-nitrophenyl)penta-2,4-dienoate ***7c***. *N*-Bromosuccinimide (5.58 g, 31.4 mmol, 1.4 equiv) was added portionwise to a solution of methyl (triphenylphosphoranylidene) acetate (9.73 g, 29.1 mmol, 1.3 equiv) in anhydrous $CHCl_3$ (125 mL) cooled to −20 °C under argon. The solution was stirred for 40 min at −20 °C, and then the solvent was evaporated under reduced pressure using a water bath at rt. CH_2Cl_2 (75 mL) and *E*-**9** (4.28 g, 22.4 mmol, 1 equiv) were then added successively to **19**. The mixture was stirred for 72 h at rt, and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel yielding the desired diene *Z*,*E*-**7c** (91:9) and the isomer *E*,*E*-**7c** as an inseparable mixture (6.21 g, 85%). R_f = 0.78 (pentane/AcOEt, 4:1); Mp = 146−148 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 3.88 (s, 3H), 7.00 (s, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.89 (s, 1H), 8.22 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 53.6, 112.8, 123.6 (2C), 130.0 (2C), 135.8, 136.7, 142.9, 144.4, 146.7, 163.7; IR (ν/cm^{-1}, neat): 3017, 2959, 2836, 1709, 1591, 1506, 1335, 1239, 1035; HRMS: (APCI) calculated for $C_{13}H_{13}BrNO_4$ (M + H)$^+$: 326.0028, found: 326.0037.

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(2Z,4E)-2-Bromo-4-methyl-5-(4-nitrophenyl)penta-2,4-dien-1-ol ***11c***. To a stirred solution of *Z,E*-**7c** and isomer (6.21 g, 19.04 mmol, 1 equiv) in anhydrous CH_2Cl_2 (190 mL) was added DIBALH (40 mL, 1 M solution in CH_2Cl_2, 40 mmol, 2.1 equiv) under argon at −78 °C. After 30 min, the reaction was quenched by the cautious addition of MeOH (1 mL). Then, a solution of HCl (150 mL, 1 M aq.) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The organic layers were brined, dried ($MgSO_4$), filtrated, and evaporated in vacuum. The crude was purified by flash chromatography on silica gel (pentane/AcOEt, 4:1) to yield *Z,E*-**11c** as a yellow powder (5.0 g, 75% over 2 steps). R_f = 0.31 (pentane/AcOEt, 4:1); Mp = 112 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 4.36 (s, 2H), 6.74 (s, 2H), 7.44 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 8.8 Hz, 2H,); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 69.2, 123.5 (2C), 125.5, 129.7 (2C), 130.7, 131.0, 137.0, 143.9, 146.3; IR (ν/cm^{-1}, neat): 3177, 2910, 2846, 1591, 1511, 1335, 1319, 1089; HRMS: (APCI) Calculated for $C_{12}H_{12}BrClNO_3$ $(M + Cl)^-$: 331.9689, found: 331.9700.

1-((1E,3Z)-4,5-Dibromo-2-methylpenta-1,3-dienyl)-4-nitrobenzene ***4c***. Triphenylphosphine (2.04 g, 7.76 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (39 mL) under argon in a 250 mL, single necked, round-bottom flask, equipped with a magnetic stirring bar. Then, bromine (400 μL, 7.76 mmol, 1 equiv) was added with a syringe at 0 °C, followed by alcohol **11c** (2.3 g, 7.76 mmol, 1 equiv) in solution in anhydrous CH_2Cl_2 (39 mL). After the mixture stirred for 10 min at 0 °C, a sat. aq solution of $NaHCO_3$ (80 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the organic layers were brined and dried on Na_2SO_4. After filtration and removal of the volatiles under reduced pressure, a yellow solid (4.96 g) containing the titled compound and triphenylphosphine oxide was recovered and used without further purification for the next step. Compound **4c** can be purified with significant loss of material by two sequential filtrations on silica gel (pentane/AcOEt, 4:1). R_f = 0.90 (pentane/AcOEt, 4:1); Mp = 78 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.17 (s, 3H), 4.37 (s, 2H), 6.78 (s, 2H), 7.45 (d, J = 8.5 Hz, 2H), 8.21 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 40.6, 121.0, 123.6 (2C), 129.8, 132.0, 133.6, 136.8, 143.5, 146.4; IR (ν/cm^{-1}, neat): 2964, 2916, 2846, 1591, 1506, 1340, 1313, 1211; HRMS: (APCI) Calculated for $C_{12}H_{11}Br_2ClNO_2$ $(M + Cl)^-$: 393.8845, found: 393.8847.

2-(2-((2Z,4E)-2-Bromo-4-methyl-5-(4-nitrophenyl)penta-2,4-dienyl)-1,3-dithian-2-yl)-6- methoxy-3,5-dimethyl-4H-pyran-4-one ***6c***. 1,3-Dithiane (2.67 g, 22.18 mmol, 2.86 equiv) was dissolved in anhydrous THF (74 mL) under an argon atmosphere in a 500 mL single necked round-bottom flask. The flask was brought to −78 °C, and *t*BuLi (13.7 mL, 1.7 M in pentane, 23.29 mmol, 3.0 equiv) was added with a syringe. The deep yellow mixture was stirred for 10 min at this temperature. Then **2** (2.04 g, 11.09 mmol, 1.43 equiv) in THF (110 mL) was added via a cannula over 10 min, and the mixture was stirred for 50 min at −78 °C during which time the solution became pale orange but remained limpid. The mixture was then cooled to −100 °C. Then, crude **4c** (2.8 g, 7.76 mmol, 1 equiv) in THF (39 mL) was added portionwise (5 portions over 20 min), and the mixture was stirred for an additional 20 min at −100 °C. The reaction was quenched by addition of 10% aq citric acid (100 mL), and the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were brined, dried (Na_2SO_4), filtrated, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel ($MeNO_2$/CH_2Cl_2, 1:2) to yield the titled compound **6c** (2.19 g, 51% yield) and recovered **4c** (430 mg, 1.6 mmol). R_f = 0.54 (pentane/AcOEt, 1:1); Mp = 49 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (s, 3H), 1.98−2.05 (m, 2H), 2.04 (s, 3H), 2.33 (s, 3H), 2.85−2.90 (m, 4H), 3.41 (s, 2H), 4.03 (s, 3H), 6.48 (s, 1H), 6.57 (s, 1H), 7.40 (d, J = 8.7 Hz, 2H), 8.17 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.8, 12.0, 17.8, 23.8, 28.4 (2C), 51.3, 55.9, 56.1, 98.9, 117.2, 122.2, 123.2 (2C), 129.4 (2C), 130.3, 137.0, 143.4, 145.9, 153.2, 161.7, 181.0; IR (ν/cm^{-1}, neat): 2910, 1650, 1607, 1586, 1511, 1340, 1308, 1164; HRMS (ESI) m/z calculated for $C_{24}H_{26}BrNNaO_5S_2$ $(M + Na)^+$: 574.0340, found: 574.0333.

1-(2-Methylpenta-1,3,4-trienyl)-4-nitrobenzene ***20***. This compound was obtained as a byproduct during the synthesis of **6c**. It was isolated from the nonpolar fraction of the purification of **6c** by preparative TLC (SiO_2, CH_2Cl_2/pentane, 1:3). R_f = 0.07 (pentane); Mp = 81 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 5.12 (d, J = 6.5 Hz, 2H), 6.05 (t, J = 6.5 Hz, 1H), 6.43 (s, 1H), 7.43 (d, J = 8.8 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6 (C-11a), 79.2 (C-8), 99.6 (C- 10), 123.5 (2C), 125.6, 129.4, 136.4, 144.6, 145.8, 211.1; IR (ν/cm^{-1}, neat): 2928, 2859, 1932, 1595, 1507, 1342, 1112; MS (ESI) m/z: 202 $(M + H)^+$; HRMS: (APCI) Calculated for $C_{12}H_{10}NO_2$ $(M - H)^-$: 200.0712, found: 200.0713.

2-((2-(6-Methoxy-3,5-dimethyl-4-oxo-4H-pyran-2-yl)-1,3-dithian-2-yl)methyl)-4-methyl-5-(4-nitrophenyl)penta-2,4-dienyl Acetate ***23***. Zn dust (312 mg, 4.77 mmol, 22 equiv) in degassed anhydrous DMF (1.5 mL) was activated with 1,2-dibromoethane (44 μL) and TFA (30 μL) under argon. To the resulting suspension was added bromomethyl acetate (381 mg, 244 μL, 2.39 mmol, 11 equiv), and the mixture was stirred for 1 h at rt. The resulting solution of **22** was transferred at rt to a solution of **6c** (120 mg, 0.217 mmol, 1 equiv), $Pd(PPh_3)_4$ (25 mg, 0.0217 mmol, 0.1 equiv), and $NaHCO_3$ (201 mg, 2.39 mmol, 11 equiv) in degassed anhydrous DMF (0.5 mL) under argon. The resulting mixture was brought to 100 °C and stirred for 45 min. After cooling to rt, sat. aq NH_4Cl solution (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were brined (3×), dried ($MgSO_4$), filtrated, and evaporated. The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 1:1) to yield **23** (24%) contaminated with coeluting isomers (yellow oil, 39 mg, 33% global yield). R_f = 0.50 (pentane/AcOEt, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (s, 3H), 1.89 (s, 3H), 1.94−2.04 (m, 2H), 2.01 (s, 3H), 2.33 (s, 3H), 2.84−2.90 (m, 4H), 3.08 (s, 2H), 4.04 (s, 3H), 4.75 (s, 2H), 6.03 (s, 1H), 6.16 (s, 1H), 7.36 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.0, 12.3, 18.6, 20.8, 24.1, 28.9 (2C), 44.2, 56.0, 57.1, 62.8, 99.4, 122.1,123.5 (2C), 128.4, 129.6 (2C), 130.5, 137.5, 139.5, 143.6, 146.2, 154.5, 161.8, 170.5, 181.0; IR (ν/cm^{-1}, neat): 2919, 1736, 1652, 1591, 1513, 1338, 1313, 1274, 1164; MS (ESI) m/z: 546 $(M + H)^+$; HRMS (ESI) m/z calculated for $C_{27}H_{32}NO_7S_2$ $(M + H)^+$: 546.1620, found: 546.1606.

(2Z,4E)-2-((2-(6-Methoxy-3,5-dimethyl-4-oxo-4H-pyran-2-yl)-1,3-dithian-2-yl)methyl)-4-methyl-5-(4-nitrophenyl)penta-2,4-dienenitrile ***24***. To a mixture of **6c** (2.19 g, 3.96 mmol, 1 equiv) and zinc cyanide (465 mg, 3.96 mmol, 1 equiv) in dry DMF (40 mL) was added tetrakis(triphenylphosphine)palladium (458 mg, 0.396 mmol, 0.1 equiv). The mixture was stirred at 120 °C under an argon atmosphere for 15 min. The mixture was cooled, and then sat. aq $NaHCO_3$ (40 mL) and Et_2O (40 mL) were added at room temperature. After the separation of the layers, the aqueous layer was back-extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was brined (3×), dried ($MgSO_4$), filtrated, and evaporated. The residue was purified by flash chromatography on silica gel (pentane/AcOEt, 1:1) to yield *Z,E*-**24** (1.40 g, 71%) and *Z,Z*-**24** (158 mg, 8%). R_f = 0.39 (pentane/AcOEt, 1:1); Mp = 63 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (s, 3H), 2.01−2.08 (m, 2H), 2.24 (s, 3H), 2.35 (s, 3H), 2.82−3.00 (m, 4H), 3.22 (s, 2H), 4.05 (s, 3H), 6.61 (s, 1H), 6.72 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.0, 12.2, 16.0, 23.8, 28.4 (2C), 45.0, 56.1, 56.5, 99.5, 105.0, 117.9, 122.5, 123.6 (2C), 130.1 (2C), 136.3, 136.4, 142.3, 146.8, 152.0, 153.0, 161.8, 181.0; IR (ν/cm^{-1}, neat): 2916, 2205, 1655, 1607, 1586, 1516, 1340, 1313, 1244, 1164; MS (ESI) m/z: 499 $(M + H)^+$, 521 $(M + Na)^+$; HRMS (ESI) m/z calculated for $C_{25}H_{27}N_2O_5S_2$ $(M + H)^+$: 499.1361, found: 499.1365.

(2Z,4E)-2-(2-Hydroxy-2-(6-methoxy-3,5-dimethyl-4-oxo-4H-pyran-2-yl)ethyl)-4-methyl-5-(4-nitrophenyl)penta-2,4-dienenitrile ***25***. In a 25 mL flask, compound *Z,E*-**24** (213 mg, 0.52 mmol, 1 equiv) was dissolved in a mixture of TFE/AcOH/H_2O (5.2 mL, 6:3:1, v/v/v). The solution was maintained at −20 °C, and bis(acetoxy)-iodobenzene (504 mg, 1.56 mmol, 3 equiv) was added. The mixture was stirred at this temperature overnight. The reaction was quenched by addition of sat. aq $Na_2S_2O_3$ (3 mL) and sat. aq $NaHCO_3$ (3 mL).

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The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were brined, dried (Na_2SO_4), filtrated, and evaporated in vacuum to afford an orange solid, which was used without further purification for the next step due to the sensitivity of the ketone.

Crude ketone (0.52 mmol, 1 equiv) was dissolved in MeOH (5 mL). The solution was brought to 0 °C, and $NaBH_4$ (22 mg, 0.57 mmol, 1.1 equiv) was added. The mixture was stirred at 0 °C for 30 min. Sat. aq NH_4Cl was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were brined, dried (Na_2SO_4), filtrated, and evaporated in vacuum. The residue was purified on silica gel (CH_2Cl_2/AcOEt/MeOH, 75:25:1) to yield **25** (107 mg, 50% yield over 2 steps). R_f = 0.27 (CH_2Cl_2/AcOEt, 1:1); Mp = 72 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78 (s, 3H), 1.90 (s, 3H), 2.24 (s, 3H), 2.72 (dd, J = 13.7, 5.8 Hz, 1H), 2.88 (dd, J = 13.7, 8.0 Hz, 1H), 4.03 (s, 3H), 5.05 (dd, J = 8.0, 5.8 Hz, 1H), 6.75 (s, 1H), 6.76 (s, 1H), 7.42 (d, J = 8.7 Hz, 2H), 8.18 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.8, 9.2, 15.9, 41.0, 55.6, 66.6, 99.7, 106.6, 118.2, 119.1, 123.5 (2C), 130.0 (2C), 135.8, 136.5, 142.5, 146.7, 150.2, 156.1, 162.5, 181.1; IR (ν/cm^{-1}, neat): 3274, 2921, 2211, 1661, 1575, 1511, 1340, 1255, 1169; HRMS (ESI) m/z calculated for $C_{22}H_{22}N_2O_6$ $(M + H)^+$: 411.1546, found: 411.1556.

2-Methoxy-3,5-dimethyl-6-((Z)-4-((E)-2-methyl-3-(4-nitrophenyl)-allylidene)-5-oxotetrahydrofuran-2-yl)-4H-pyran-4-one ***27***. To a solution of alcohol **25** (155 mg, 0.378 mmol, 1 equiv) in $MeNO_2$ (7.5 mL) was added trifluoromethanesulfonic acid (283 mg, 167 μL, 1.89 mmol, 5 equiv) at rt. The mixture was stirred for 3 h. Acetic acid (7.5 mL) and H_2O (7.5 mL) were then added to the resulting imino ether **26**, and the mixture was stirred for an additional 6 h. Sat. aq $NaHCO_3$ (130 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was brined, dried ($MgSO_4$), filtrated, and evaporated in vacuum. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/AcOEt, 4:1) to yield **27** (100 mg, 65% yield). R_f = 0.42 (CH_2Cl_2/AcOEt, 1:1); Mp = 65−66 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H), 2.04 (s, 3H), 2.24 (s, 3H), 3.19 (ddd, J = 16.9, 5.2, 2.3 Hz, 1H), 3.44 (ddd, J = 16.9, 8.6, 2.3 Hz, 1H), 3.92 (s, 3H), 5.68 (dd, J = 8.6, 5.2 Hz, 1H), 6.81 (br s, 1H), 6.85 (s, 1H), 7.49 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.9, 9.4, 18.3, 34.8, 55.5, 71.1, 100.3, 120.8, 123.4, 123.5 (2C), 130.0 (2C), 134.1, 136.2, 143.1, 143.5, 146.6, 151.6, 162.0, 166.8, 180.0; IR (ν/cm^{-1}, neat): 2926, 1757, 1666, 1591, 1511, 1340, 1260, 1164; MS (ESI) m/z: 410 $(M - H)^-$; HRMS (ESI) m/z calculated for $C_{22}H_{22}NO_7$ $(M + H)^+$: 412.1403, found: 412.1396.

2-((4Z)-5-(Benzhydrylimino)-4-((E)-2-methyl-3-(4-nitrophenyl)-allylidene)tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4H-pyran-4-one ***28***. To a mixture of alcohol **25** (100 mg, 0.244 mmol, 1 equiv) and diphenylmethanol (45 mg, 0.244 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added trifluoromethanesulfonic acid (183 mg, 108 μL, 1.22 mmol, 5 equiv) at rt. The mixture was stirred at this temperature for 2 h. Sat. aq $NaHCO_3$ (10 mL) was then added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were brined, dried ($MgSO_4$), filtrated, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/AcOEt, 4:1) to yield compound **28** (77 mg, 55% yield). R_f = 0.36 (pentane/AcOEt, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.03 (s, 3H), 2.25 (s, 3H, H), 3.27 (ddd, J = 16.2, 5.1, 2.3 Hz, 1H), 3.35 (ddd, J = 16.2, 8.6, 2.3 Hz, 1H), 3.43 (s, 3H), 5.57 (dd, J = 8.6, 5.1 Hz, 1H), 6.02 (s, 1H), 6.51 (br s, 1H), 7.11 (s, 1H, H-12), 7.05−7.35 (m, 10H), 7.48 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.8, 9.3, 19.4, 36.6, 55.0, 64.9, 72.5, 99.8, 119.7, 123.5 (2C), 126.53, 127.3, 127.4, 128.0, 128.1, 128.6, 129.8 (2C), 130.51, 135.7, 137.0, 144.2, 144.4, 144.6, 146.1, 153.0, 154.6, 161.9, 180.1; IR (ν/cm^{-1}, neat): 2926, 1669, 1595, 1515, 1341, 1258, 1167; MS (ESI) m/z: 577 $(M + H)^+$; HRMS (ESI) m/z calculated for $C_{35}H_{33}N_2O_6$ $(M + H)^+$: 577.2339, found: 577.2363.

2-((3Z,5E)-1-Hydroxy-3-(hydroxymethyl)-5-methyl-6-(4-nitrophenyl)hexa-3,5-dienyl)-6-methoxy-3,5-dimethyl-4H-pyran-4-one ***5c***. To a stirred solution of lactone **27** (100 mg, 0.243 mmol, 1 equiv) in anhydrous THF (2.4 mL) at −78 °C was added $LiBHEt_3$ (608 μL, 1 M in THF, 0.608 mmol, 2.5 equiv). The mixture was stirred at this temperature for 1 h. Sat. aq NH_4Cl (5 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The organic layers were brined, dried ($MgSO_4$), filtrated, and evaporated in vacuum. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/AcOEt, 1:2) to yield compound **5c** (62 mg, 62% yield). R_f = 0.31 (AcOEt); Mp = 176 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78 (s, 3H), 1.91 (s, 3H), 1.96 (s, 3H), 2.62 (dd, J = 13.8, 3.3 Hz, 1H), 2.76 (dd, J = 13.8, 8.5 Hz, 1H), 4.02 (s, 3H), 4.33 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.98 (dd, J = 8.5, 3.3 Hz, 1H), 5.95 (s, 1H), 6.44 (s, 1H), 7.38 (d, J = 8.6 Hz, 2H), 8.17 (d, J = 8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 6.9, 9.3, 19.0, 41.9, 55.6, 61.5, 68.8, 99.5, 118.1, 123.5 (2C), 128.1, 129.6 (2C), 135.5, 137.5, 138.0, 144.2, 146.0, 157.3, 162.6, 181.3; IR (ν/cm^{-1}, neat): 3303, 2933, 1658, 1569, 1512, 1335, 1257, 1166; HRMS (ESI) m/z calculated for $C_{22}H_{26}NO_7$ $(M + H)^+$: 416.1709, found: 416.1693.

*(±)-Aureothin (****1****).* Compound **5c** (56 mg, 0.135 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (0.75 mL). The solution was brought to −78 °C, and Et_3N (27 mg, 36 μL, 0.27 mmol, 2 equiv) was added. Then, a solution of mesyl chloride (1.5 mL, 0.09 M in CH_2Cl_2, 0.135 mmol, 1 equiv) was slowly added with a syringe pump (1.5 mL·h^{-1}). After the addition, the mixture was maintained for 10 min at −78 °C and was then allowed to warm to 0 °C. tBuOH (1.5 mL) was added followed by freshly sublimated tBuOK (45 mg, 0.405 mmol, 3 equiv). After 10 min, the reaction was quenched by the addition of aq 10% citric acid solution, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were washed with sat. aq $NaHCO_3$ solution, brine, dried (Na_2SO_4), filtrated, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 10:1) to yield **1** (27 mg, 51%) and unreacted diol **5c** (7 mg, 13%). The data were in perfect agreement with a sample of aureothin prepared by biotransformation. R_f = 0.69 (CH_2Cl_2/EtOAc, 1:1); (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.00 (s, 3H), 2.03 (s, 3H), 2.94 (dd, J = 16.0, 6.2 Hz, 1H), 3.05 (dd, J = 16.0, 7.0 Hz, 1H), 3.93 (s, 3H), 4.72 (d, J = 14.0 Hz, 1H), 4.85 (d, J = 14.0 Hz, 1H), 5.12 (t, J = 7.0 Hz, 1H), 6.19 (br s, 1H), 6.35 (s, 1H), 7.38 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 7.3, 9.8, 18.1, 38.7, 55.6, 70.5, 73.7, 100.5, 120.1, 124.0, 126.3, 128.7, 129.95, 138.9, 141.0, 144.55, 146.5, 155.0, 162.4, 180.9; HRMS (ESI) m/z calculated for $C_{22}H_{24}NO_6$ $(M + H)^+$: 398.1604, found: 398.1604.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00878.

^{1}H and ^{13}C spectra for all compounds and HPLC data for **5a** (PDF)

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Notes

The authors declare no competing financial interest.

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